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<b>(21) International Application Number:</b> PCT/GB97/02349 <b>(22) International Filing Date:</b> 1 September 1997 (01.09.97)  <b>(30) Priority Data:</b> 9618341.3 3 September 1996 (03.09.96) GB  <b>(71) Applicant (for all designated States except US):</b> SCOTIA HOLDINGS PLC [GB/GB]; Weyvern House, Weyvern Park, Portsmouth Road, Peasmarsh, Guildford, Surrey GU3 1NA (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BRUNES, Birgitta [SE/SE]; Fimta, S-640 23 Valla (SE). BRUNES, Christian [SE/SE]; Fimta, S-640 23 Valla (SE).  <b>(74) Agent:</b> FARWELL, William, Robert; Phillips & Leigh, 7 Staple Inn, Holborn, London WC1V 7QF (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> METHOD OF TREATMENT  <b>(57) Abstract</b>  Medicament for use in a syndrome shown in multiple sclerosis, depression and other conditions, and also in tinnitus and sterile prostatitis unassociated with such conditions, comprising a cholinergic drug which either activates acetyl choline receptors or inhibits the degradation of acetyl choline.		

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## METHOD OF TREATMENT

### Field of Invention

The invention relates to drug treatments.

### Cholinergic Drugs

Cholinergic drugs are compounds which enhance or imitate the actions of acetyl choline, a natural transmitter in the central and peripheral nervous systems.

Drugs which enhance the actions of acetyl choline do so by reducing its rate of inactivation, usually by inhibiting the actions of enzymes known as cholinesterases which normally break down acetyl choline very rapidly. Such anti-cholinesterases and related drugs may thus enhance many of the actions of acetyl choline. Examples are physostigmine, neostigmine, edrophonium, pyridostigmine, demacarium and ambeconium.

Drugs which imitate the actions of acetyl choline tend to fall into two main classes, nicotinic and muscarinic. These classes arise because there are two major classes of receptors which can both be activated by acetyl-choline. One class can also be readily activated by the alkaloid muscarine and so is called muscarinic, while the other class can readily be activated by nicotine and so is called nicotinic. Examples of cholinergic drugs which can imitate some or all of the actions of acetyl choline are methacholine chloride, carbachol chloride, bethanechol chloride, nicotine, pilocarpine, muscarine and arecoline.

### Present Work

For over twenty years the inventors have been involved in the treatment of patients with multiple sclerosis, other neurological disorders or psychiatric disorders, including clinical depression. Some patients with these diseases, and also some patients who do not

appear to have such diseases, may present with one or more of a range of signs and symptoms, set out below. We have unexpectedly found these signs and symptoms to respond to cholinergic drugs.

The invention therefore lies broadly in the use of such drugs in the treatment of conditions showing these signs and symptoms as set out in the claims herein.

In particular we have found that in some multiple sclerosis patients these signs and symptoms may be exacerbated by treatment with anti-depressants, whether with or without additional treatment with neurotransmitter precursors such as L-phenylalanine, L-tyrosine, L-DOPA and tryptophan, and with vitamin B12, such additional treatment being of value in treating the underlying multiple sclerosis. The cholinergic drugs may be used in this situation.

Further and separately we have found that patients with tinnitus or with sterile prostatitis independently of multiple sclerosis and the other conditions discussed may respond to the cholinergic drugs.

Some of the symptoms and signs which we have observed and which respond to cholinergic drugs are similar to those which may follow the administration of anticholinergic compounds such as atropine. However, we emphasise that these symptoms and signs are not caused only by the administration of anticholinergic drugs but occur either spontaneously, or occur or are exacerbated by treatment with compounds such as antidepressants which may enhance the effects of other transmitter systems such as those involving noradrenaline, adrenaline, dopamine and serotonin. Other of the symptoms have not to our knowledge previously been described in the context of side effects of anticholinergic agents.

## The Syndrome

There follow the main symptoms which indicate to us that a patient will respond to cholinergic agents:

1. Dry mouth with inadequate salivation. Very occasionally, the opposite symptom of excessive salivation may indicate the possibility of a response to a cholinergic drug.
2. Dry eyes with inadequate tear production.
3. Sensitivity to light, largely because of inadequate pupillary constriction as light intensity increases.
4. Cold hands and cold feet indicating inadequate circulation to the skin of the periphery.
5. A raised and occasionally irregular heart rate.
6. Bladder disturbances, largely related to inadequate bladder tone. As a result the bladder may not empty fully leading to urinary retention, a frequent sense of need to urinate (urgency), urinary infections, and difficulty in starting urination.
7. Constipation and slow bowel movements. As with salivation, occasionally the opposite symptom, diarrhoea, may indicate a possible responder to cholinergic drugs.
8. A feeling of deep cold (cold into the bones) which is distinct from the cold hands and feet described in item 4.
9. Patients may often be relatively slim in relation to their levels of activity and food intake.
10. There may be disturbances in the sensory system with a burning sensation and a sensation that the muscles of the arms and trunk are pressing from within against the surface of the skin. In patients with multiple sclerosis this is sometimes known as the "MS hug", a feeling that one is being hugged in the absence of any external pressure.
11. A feeling of the mind not working, of difficulties in concentration and memory.
12. A feeling of stiffness and rigidity in the muscles.
13. Tinnitus.
14. Sterile prostatitis.

### Further Discussion

Some individuals with the syndrome may display all or most of the features, while others may exhibit only one or a few features. Particularly significant symptoms are those numbered 1, 6, 7, 10 and 12. Tinnitus and sterile prostatitis may also be treated even in patients without multiple sclerosis, depression or the other conditions primarily discussed herein. The syndrome is not due to the administration of anticholinergic drugs, and some features of it, such as the tinnitus, sterile prostatitis and sensory experiences do not appear to have been described in connection with the administration of anticholinergic drugs. The syndrome can occur in individuals who have no other known illness but it is much more likely to be present for example in those who have multiple sclerosis or who are depressed. In such patients it may be exacerbated by the administration of antidepressants and by the administration of precursors of adrenergic and serotonergic transmitters such as L-phenylalanine, L-tyrosine, L-DOPA and L-tryptophan. Any type of antidepressant may precipitate or exaggerate the syndrome, including tricyclic and tetracyclic compounds, selective and non-selective monoamine oxidase inhibitors and the selective serotonin reuptake inhibitors. We have particularly observed the syndrome in patients with multiple sclerosis given lofepramine.

We have now observed several hundred patients with this syndrome. We have unexpectedly found that many, and in some patients all, of the symptoms may be relieved by the administration of cholinergic drugs, compounds which imitate acetyl choline or which reduce its inactivation. In particular we have found that compounds which have combined muscarinic and nicotinic actions or predominantly nicotinic effects are specially effective, although relatively pure muscarinic drugs may have effects on some symptoms. We have found that carbachol is the preferred drug although nicotine from smoking or from nicotine patches may also be effective. Other drugs which may be used for some or all of the symptoms include any drug which exerts agonist effects at muscarinic or nicotinic receptors, such as carbachol, bethanechol, methacholine, any other choline esters, lobeline, pilocarpine, arecoline, cisapride, or any drug which enhances cholinergic activity by inhibiting

cholinesterase, such as neostigmine, physostigmine, edrophonium and tacrine. The drugs may be administered by appropriate routes and in appropriate doses, according to the nature of the drug as will be known to those skilled in the art. The routes include oral, sub-cutaneous, other parenteral, topical and ocular routes although in most situations the oral, sub-cutaneous or topical routes are to be preferred. For example, carbachol may be administered in doses of 0.1 - 10 mg orally or sub-cutaneously several times a day as required with a maximum dose in the 30 - 100 mg per day range. In the future slow release formulations or novel derivatives of drugs which act on nicotinic and muscarinic receptors may be developed and such may be used in the present context. More highly lipophilic drugs which more readily penetrate the brain may be of particular value.

### Examples

The following are of value for all the purposes set out herein:

1. Tablets containing 2mg carbachol to be administered as required.
2. Sterile injectable carbachol solution containing 5mg carbachol/ml to be given subcutaneously.
3. Tablets containing 5mg bethanechol to be administered as required
4. Injectable bethanechol chloride solution containing 5mg/ml to be given subcutaneously.
5. Nicotine tablets or nicotine gum each unit containing 4mg nicotine.

### Case Histories

The following illustrate treatment according to the invention.

A 33 year old woman with multiple sclerosis had a dry mouth, an inability to empty her bladder normally leading to recurrent urinary infections, constipation and occasional tinnitus. The patient was treated with lofepramine, 70 mg twice daily, and these symptoms

became worse with a failure of normal tear production, sensitivity to light and cold extremities. Treatment with carbachol, 2 mg taken orally 4 hourly during the day time relieved the symptoms and at the same time produced an improvement in the fatigue, stiffness, muscle spasms and walking difficulties produced by the multiple sclerosis.

A 44 year old male with multiple sclerosis had inadequate bladder function with urinary retention, a dry mouth and eyes; a sensation of muscles pressing against his skin; muscular stiffness and rigidity, and prostatitis with no demonstrable infectious organisms in the prostatic fluid (sterile prostatitis). Treatment with carbachol in a dose of 3 mg four times a day produced substantial relief of all these symptoms.

A 55 year old man without multiple sclerosis had tinnitus of unknown origin with no known precipitating cause. Treatment with carbachol, 2 mg every 4 hours, abolished the tinnitus.



## CLAIMS

1. The use of a cholinergic drug, namely a drug which imitates or enhances the actions of acetyl choline either by activating acetyl choline receptors or by inhibiting the degradation of acetyl choline, for preparation of a medicament for treatment of the syndrome described herein, particularly when characterised by symptoms 1, 6, 7, 10 and 12, and such treatment wherein such medicament is used.
2. Use or treatment according to claim 1, for the syndrome when in patients with neurological disorder(s).
3. Use of treatment according to claim 2, for the syndrome when in patients with multiple sclerosis.
4. Use or treatment according to claim 1, for the syndrome when in patients who are depressed or suffering from other psychiatric disorder.
5. Use or treatment according to claim 3 or 4, for the syndrome when in patients who are receiving multiple sclerosis or depression therapy with antidepressants, particularly lofepramine, with or without the addition of neurotransmitter precursors such as L-phenylalanine, L-tyrosine, L-DOPA and L-tryptophan.
6. The use of a cholinergic drug, as defined in claim 1, for preparation of a medicament for treatment of tinnitus in any patient, and tinnitus treatment wherein such medicament is used.
7. The use of a cholinergic drug, as defined in claim 1, for preparation of a medicament for treatment of sterile prostatitis in any patient, and sterile prostatitis treatment wherein such medicament is used.

8. Use or treatment according to any of claims 1 to 7, where the cholinergic drug is carbachol or other choline ester or agent which activates nicotinic and/or muscarinic receptors, preferably nicotinic receptors alone or both nicotinic and muscarinic receptors.